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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,553	04/24/2001	Hikaru Takakura	TAKAKURA=1A	4153

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EXAMINER

RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
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1652

16

DATE MAILED: 08/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/841,553

Applicant(s)

TAKAKURA ET AL.

Examiner

Manjunath N. Rao, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-5 and 7-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 2,3 and 5 is/are allowed.
- 6) ☒ Claim(s) 4 and 7-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 April 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

Claims 2-5, and 7-12 are currently at issue and are present for examination.

Applicants' amendments and arguments filed on 4-24-03, paper No.8, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 and claims 8, 10 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 is drawn to a polynucleotide encoding a hyperthermostable protease comprising the amino acid sequence of SEQ ID NO:6. however, a perusal of the sequence listing indicates that SEQ ID NO:6 is a polynucleotide sequence and not a polypeptide sequence. Therefore, it is not clear to the Examiner as to whether applicants are claiming a polynucleotide or a polypeptide sequence.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 9, 11-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide with SEQ ID NO:2 or 6 encoding a

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polypeptide with SEQ ID NO:1 or 5 respectively, having hyperthermostable protease activity, does not reasonably provide enablement for any or all polynucleotides encoding any or all hyperthermostable proteases wherein said polynucleotides can hybridize to either SEQ ID NO:2 or 6 when hybridization is carried out by incubating in 6X SSC at 50 °C and washing with 2X SSC at 37 °C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 4, 9, 11-12 are so broad as to encompass any or all polynucleotides which encodes any or all hyperthermostable proteases and vectors and host cells comprising such polynucleotides and method of making said proteases. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotide sequences that are broadly encompassed by the claims.

Claims 4, 9, 11-12 are drawn to polynucleotides that are identified by their ability to hybridize to SEQ ID NO:2 or 6 under low to medium stringency conditions. Under such conditions, polynucleotides that have as low as 40-50% sequence identity SEQ ID NO:2 or 6 and isolated from any or all sources including all microorganisms, plants and animals, including

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any variant and mutant or recombinant will hybridize to SEQ ID NO:2 or 6. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of just two hyperthermostable proteases isolated from a single source.

Applicants claims also encompass polynucleotides encoding variants of the hyperthermostable protease whose encoding polynucleotides are modified. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only two proteases. It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides by making such changes. The specification is limited to teaching the use of SEQ ID NO: 6 and 2 as polynucleotides encoding hyperthermostable protease with SEQ ID NO:1 and 5 but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the

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specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or modifications of nucleotides, as encompassed by the instant claims, and the base changes within a nucleic acid's sequence that can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given DNA to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA encoding a protein having hyperthermostable protease activity because the specification does not establish: (A) a rational and predictable scheme for isolation and characterization of polynucleotides encoding a hyperthermostable protease from any or all sources; (B) regions of the DNA sequence which may be modified without effecting the above mentioned activity/utility; (C) the general tolerance of any hyperthermostable protease encoding DNA sequence to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any nucleotide in the polynucleotide encoding a hyperthermostable protease with an expectation of obtaining the desired biological function and utility; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope

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of the claims broadly including any or all DNA encoding hyperthermostable protease. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of DNAs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action applicants have traversed the above rejection arguing that the rejection is obviated by their amendments (deletion of “functional equivalent thereof”) and the recitation of specific stringent conditions. Examiner respectfully disagrees with such an argument that the amendments are persuasive to overcome the above rejection. This is because, even though applicants have deleted the “functional equivalents” phrase, claims are still broad as the hybridization conditions stipulated in the claims are any where from low to medium stringency conditions and not the high stringency conditions. The hybridization temperature of 50 ° C with a wash temperature of 37 ° C is considered as low or at best medium stringency conditions in the art. Either a hybridization temperature of 65 ° C or wash conditions in a low salt buffer at 65 ° C is generally considered as high stringency conditions in the art. In view of this fact and as explained in the above rejection, claims continue to be too broad and therefore the above rejection is maintained.

Claims 4, 9, 11-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

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had possession of the claimed invention. These claims are directed to a genus of DNA molecules encoding a hyperthermostable protease capable of hybridizing to the polynucleotides encoding polypeptides with SEQ ID NO:1 or 5 under low to medium stringency conditions.

The specification does not contain any disclosure of the structure of all DNA sequences claimed. The genus of cDNAs that comprise these above DNA molecules is a large variable genus with the potentiality of having many different structures. Therefore, many structurally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a two species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office action applicants have traversed the above rejection arguing that the rejection is obviated by their amendments (deletion of “functional equivalent thereof”) and the recitation of specific stringent conditions. Examiner respectfully disagrees with such an argument that the amendments are persuasive to overcome the above rejection. Applicants further refer to the “Guidelines” and recite the following,

--Now turning to the genus analysis, a person of skill
In the art would not expect substantial variation among
Species encompassed within the scope of the claims
Because the highly stringent hybridization conditions
Set forth in the claim yield structurally similar DNAs.
Thus, a representative number of species is disclosed,

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since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge....of the claimed invention.--

Applicants that the fact situation in the present application is similar to the Example 9 discussed above, and accordingly the invention is adequately described. Examiner respectfully disagrees with such an argument. This is because the fact situation is not identical to the situation in the above example as the hybridization conditions recited in the claims cannot be considered as "highly stringent" (see above) but at best can be considered as "medium stringent" conditions. Therefore, claims continue to encompass polynucleotides whose structure have not been described. Therefore, the above rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 4, 9, 11-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Yamamoto et al. (WO 95/34645, Dec 21, 1995). This rejection is based upon the public availability of a printed publication. Claims 4, 9, 11-12 of the instant application is drawn to polynucleotides encoding a hyperthermostable protease wherein said polynucleotide hybridizes to the polynucleotide with either SEQ ID NO:2 or 6 under a medium stringent condition comprising incubation in 6X SSC at 50 ° C followed by wash in 2X SSC at 37 ° C. Yamamoto et al. disclose polynucleotides which have a 100% match over 550 to 600 nucleotide stretch to SEQ ID NO:2 and a 100%

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match over at least 300 nucleotide stretch to SEQ ID NO:6, wherein said reference polynucleotides encode a hyperthermostable protease. Such polynucleotides can easily hybridize to SEQ ID NO:2 or 6 under the conditions described in the claim. Therefore, Yamamoto et al. anticipate claims 4, 9, 11-12 as written.

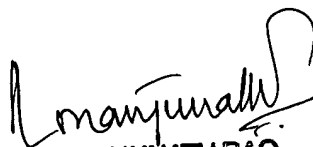
Conclusion

Claims 2, 3 and 5 are allowable.

Examiner has withdrawn the previous rejection of claims 2, 4-5, 7, 9-10 under 35 U.S.C. 103(a) as obvious over Klingenberg et al. in view of the claim amendments and arguments presented by the applicants.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

Manjunath N. Rao
August 6, 2003


MANJUNATH RAO
PATENT EXAMINER